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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,203	12/06/2000	Markus Kalkum	1539-00	7336

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EXAMINER	
GORDON, BRIAN R	

ART UNIT	PAPER NUMBER
1743	

DATE MAILED: 09/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,203	KALKUM ET AL.	
	Examiner	Art Unit	
	Brian R. Gordon	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8-15-05* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,23-30,36 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *20 and 23-29* is/are allowed.

6)☒ Claim(s) *30 and 36-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 December 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 15, 2005 has been entered.

Response to Arguments

1. Applicant's arguments, see amendment, filed July 18, 2005, with respect to the rejection(s)of claim(s) 30 and 32-38 under 102 and 103 respectively have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Howe et al. US 5,976,369.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 30 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tajima in view of Little et al. US 6,024,925 in further view of How et al. US 5,976,369.

Tajima teaches a method making use of a pipette device which sucks a liquid containing a target high molecular substance via a chip detachably set in a sucking port or a discharging port of a liquid sucking/discharging line from inside of a vessel and transfers the liquid or the target high molecular substance to a target next processing position, and the chip has the sucked target high molecular substance deposited on magnetic particles (solid carrier material) and/or separated with a filter set in the chip. Namely, it is possible to automatically execute with high precision the works of quantifying, separating, taking out, pipetting, clarifying, condensing, diluting a liquid or a

target high molecular substance as well as works of extracting, recovering, and isolating the substance by controlling the pipette device's operations for sucking and discharging the liquid and magnetic particles with a magnetic body and/or by a combination of a magnetic body and a filter (pourous carrier material).

The target high molecular substance is a useful substance such as antibiotics, genetic substances such ad DNA, or an immunological substance such as antibody. For this reason, the present invention is well suited to works of separating, taking out, pipetting, clarifying, condensing, diluting and/or works of capturing, extracting, isolating, amplifying, labelling, and measuring molecule level organisms or microorganisms such as cells, DNA, RNA, mRNA, plasmid, virus, and bacteria or certain high molecular substance, and a target high molecular substance can be obtained without depending on the conventional centrifugation.

By having a target high molecular substance or a substance bonded to a target high molecular substance absorbed or bonded to a surface of each magnetic particle used for the purpose of the present invention, the target high molecular substance can be obtained without executing centrifugation.

In the present invention, in a case where the above-described magnetic particles are used, controls are provided so that the magnetic particles are absorbed onto an internal wall of a chip due to a magnetic force working from outside of the chip, or so that, if effect of the magnetic force is weak or not present, the magnetic particles are held separable from the internal surface of the chip, it is possible to control capture of

target high molecular substance and separation of the same from foreign materials with high precision.

There is provided a liquid processing apparatus making use of a pipette device (microdosing device) comprising a liquid sucking/discharging line which can move in the horizontal line and is maintained at a specified position so that it can move in the vertical direction, a plurality of chips required for processing one type of liquid and provided along the horizontal line in which this sucking/discharging line moves, a vessel with the liquid accommodated therein, one or more filter holders each having a filter set therein required for the processing described above, one or more vessels each accommodating therein other types of liquid required for the processing above, a vessel in which a liquid containing magnetic particles is accommodated, and a magnetic body for attracting the magnetic particles onto an internal surface of the chip in the process of sucking or discharging a solution containing the magnetic particles, and the liquid sucking/discharging line is transferred according to instructions from a control unit to execute required processing for a liquid or a target high molecular substance contained in the liquid, and for this reason it is possible to execute such works as quantifying, separating, taking out, pipetting, clarifying, condensing, diluting a target high molecular substance and also such complicated works as extracting, recovering, and isolating the target high molecular substance with very simple configuration in succession and automatically.

In a case where the magnetic body is built with a permanent magnet, a surface of the **permanent magnet** (drive device) contacting a chip is formed according to an

external form of the chip and the chip is movably provided in a direction perpendicular to the longitudinal direction of the chip, so that it is possible not only to completely capture magnetic particles, but also to prevent adverse effects by diffusion and movement of the magnetic particles in association with the magnet without fail.

The magnetic body may also be built with an **electric magnet** (drive device) in place of the permanent magnet described above with a surface thereof contacting a chip formed according to an external form of the chip, and is provided so that the electric magnet generates a magnetic force when it contacts outside of the chip and also can move, when degaussed, in a direction perpendicular to the longitudinal center line of the chip or in a range including the direction, and for this reason magnetic particles are attracted in association with movement of the magnetic body along the longitudinal center line of the chip so that it is possible to prevent the magnetic particles from going out of control and control over the magnetic particles from being lost, which makes it possible to realize complete attraction of the magnetic particles.

Tajima also teaches a step of subjecting DNA refined through the reaction steps as given in relation to such works as extracting, recovering, isolating or amplifying with PCR or to control for temperature thereof.

Namely, in a case where such works as extracting, recovering, or isolating by making use of this pipette device with magnetic particles G with DNA or DNA-bonded substance bonded to the surface, as shown in step 14 in FIG. 13, at first the pipette nozzle P is moved upward and then transferred to just above a fourth cell C_4 with the second filter holder H_2 left in cell C_3 via a filter holder removing body E_2 having the

same configuration as that of the filter holder removing body E_1 and the sucked DNA solution is discharged into the cell C_4.

A required quantity of reaction liquid containing magnetic particles G with DNA or DNA-bonded substance bonded to the surface thereof has been supplied into this cell C_4, and when the DNA solution is discharged into the reaction liquid, a reaction between DNA fragments and the magnetic particles G is started.

The chip T_3 with the DNA solution having been discharged into the cell C_4 is removed from the lower edge section of the pipette nozzle P according to the processing sequence like in a case of the chip T_1 or chip T_2, and is aborted.

It is needless to say that then the chip T_4 is set in the lower edge section of the pipette nozzle P according to the processing sequence as described above.

Then, after a certain period of time has passed, the pipette nozzle P goes downward and steeps the chip T_4 into the reaction liquid, the magnetic body M contacts the intermediate diameter section K_{12} of the chip T_4, the works of sucking and discharging the liquid by the pipette nozzle P is executed at least once according to the necessity, and separation between the magnetic particles and the reaction liquid is executed (step 15). Then the sucking and discharging work is executed to a slow speed so that almost all the magnetic particles are captured. In this case, it is important for completely attracting the magnetic particles to provide controls over the sucking and discharging operations so that the final liquid surface of the reaction liquid sucked or discharged

passes through an area effected by a magnetic force generated by the magnetic body M.

Tajima does not teach that the device comprises pipettes with a volume of less than 10 microliters.

Little et al. discloses systems and methods for preparing a sample for analysis, and more specifically to systems and methods for dispensing low volumes of fluid material onto a substrate surface for generating an array of samples for diagnostic analysis.

The invention can comprise an apparatus for dispensing a fluid in chemical or biological procedures into one or more wells of a multi-well substrate. The apparatus can include a housing having a plurality of sides and a bottom portion having formed therein a plurality of apertures, the walls and bottom portion defining an interior volume, a plurality of fluid transmitting vesicles, mounted within the apertures, having a fluid holding chamber disposed in communication with the interior volume of the housing, and a fluid selection and dispensing means in communication with the interior volume of the housing for variably selecting an amount of the fluid loaded within the fluid holding chambers of the vesicles to be dispensed from a single set of the plurality of fluid transmitting vesicles. Accordingly, the dispensing means dispenses a selected amount of the fluid into the wells of the multi-well substrate when the apparatus is disposed over and in registration with the substrate (column 5, lines 8-23).

Each of the holding chambers 64A-64D is sufficiently small to allow the chambers to be filled by capillary action. In such a practice, the pin assembly can

consist of an array of narrow bore needles, such as stainless steel needles, that extend through the apertures of the lower block 54. The needles that are dipped into source solutions will be filled by capillary action. In one practice, the length of capillary which is to be filled at atmospheric pressure is determined approximately by an equation. Thus the volume of fluid held by each vesicle can be controlled by selecting the dimensions of the interior bore. It is understood that at room temperature water will fill a 15 cm length of 100 μm radius capillary. Thus, a short bore nanoliter volume needle will fill to full capacity, but should not overflow because the capillary force is understood to be too small to form a meniscus at the top of the needle orifice. This prevents cross-contamination due to spillage. In one embodiment, the vesicles of the pin assembly can be provided with different sized interior chambers for holding and dispensing different volumes of fluid (column 9, lines 40-67).

The invention allows for rapidly dispensing definite and controlled volumes of analyte material. In particular these processes allow **for dispensing sub to low nanoliter volumes of fluid**. These low volume deposition techniques generate sample arrays well suited for analysis by mass spectrometry (column 11, lines 50-57).

In one example a 10 X 10 array of 0.2-20 nL droplets were dispensed. The capillary was emptied by application of positive pressure, optionally rinsed with H2O, and led to the source oligo plate where about 5 μL of 0.05-2.0 μM synthetic oligo were drawn. The capillary was then rastered in series over each of the matrix spots with 0.2-20 nL aqueous solution added to each (column 15, lines 27-34).

The capillary device may also comprise a transducer element selected from the group consisting of a piezoelectric, electric, electrorestrictive, magnetorestrictive, and electromechanical transducer (claim 53).

It would have been obvious to one of ordinary skill in the art at the time of the invention to recognize that the pipette device of Tajima et al. may be manufactured from the material and process of that as taught by Little et al. in order to provide sufficient control over the volume of sample material that is dispensed onto the surface of the substrate and to accurately reproduce the dispensed sample volumes.

The combined teachings of Tajima et al. in view of Little et al. do not disclose a driving device comprises two magnets.

Howe et al. disclose an apparatus for performing the magnetic separation method which apparatus comprises an array of vessels each to contain a liquid suspension of magnetically attractable particles; a pipetting system for transferring liquid to and from the array of vessels; and a magnet system mounted for movement relative to the array of vessels, so as to be either free of the array of vessels or engaged with the array of vessels in one of two positions.

FIGS. 4a and 4b. The magnet system comprises a carrier plate 1 of aluminium; a backflow plate 2 of iron overlying the carrier plate; a row of permanent magnets 3 of Nd, Fe, B; a field concentrator plate 4 of iron overlying the permanent magnets; and a cover plate 5 of aluminium overlying the field concentrator plate. Each permanent magnet is positioned on the back flow plate with its N-S axis perpendicular to the back flow plate, the polarity of each permanent magnet being opposite to that of its neighbour or

neighbours. The permanent magnets are spaced apart at regular intervals to define between them work stations, of which two are shown in FIG. 4a. A hole is provided through the field concentrator plate and the overlying cover plate for locating a vessel at each work station. A Sarstedt tube 6 is shown in position at one work station, and an Elkay tube 7 in position at the other.

It would have been obvious to one of ordinary skill in the art at the time of the invention to further modify the drive device of Tajima et al. by incorporating a second magnet at V where the opposite pole is facing that of M in order to allow for the magnetic particles to be separated out on both sides of the pipette.

Allowable Subject Matter

7. Claims 20 and 23-29 are allowed.

8. The following is a statement of reasons for the indication of allowable subject matter: The prior art of record does not teach nor fairly suggest a method for processing at least one substance in a reservoir of a microdosing device, said microdosing device being a micropipette or a microdispenser and said reservoir having an outlet being adapted for microdroplet delivery comprising the steps of: arranging a solid carrier material as a solid phase with a binding-active surface in the reservoir, said carrier material being held with a drive device located outside said reservoir; collecting the substance in the reservoir by repeatedly performing the steps of uptaking a solution or suspension liquid with the substance into the reservoir, repeatedly moving the carrier material in the reservoir with said drive device and binding the substance to a surface of the carrier material and delivering the remaining liquid from

the reservoir; and uptaking an elution agent separating the bound substance from the carrier material or a reaction partner reacting with the substance in the reservoir.

Conclusion

2. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Schmitt et al. and a'Brassard disclose magnetic separation devices.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian R. Gordon whose telephone number is 571-272-1258. The examiner can normally be reached on M-F, with 2nd and 4th F off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on 571-272-1267. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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